The specification has been carefully reviewed and editorial changes have been effected. All of the changes are minor in nature and therefore do not require extensive discussion. Specifically, the specification headings have been amended in conformance with U.S. practice.

Claims 14, 15 and 17-29 have been cancelled without prejudice. Further, claims 13, 16, 30 and 31 have been amended, and new claims 32-34 have been added. The claim amendments and new claims have been presented to put the claims in better form under U.S. practice and should not be construed to narrow the scope of the claims with the exception of the phrase "(iii) retaining the calcium channel modulatory function of the peptide of SEQ ID No. 1." Support for the claim amendments and new claims is readily apparent from the teachings of the specification and the original claims. Specifically, support for new claims 33 and 34 is found in the original antibody claims, original claim 5 and page 6, lines 14-26, of the specification. Please note that new claims 33 and 34 have been present to further protect specific embodiments of the claimed peptide.

With regard to the restriction requirement, Applicants hereby affirm the election of Group I, claims 13-17 and 28-31. It is noted that this election is made by the Applicants while retaining their right to file a divisional application directed to the non-elected subject matter with the protection afforded by 35 USC 121. Claims 18-27, directed to non-elected subject matter, have been cancelled without prejudice and will be later filed in a divisional application.

Before specifically addressing the rejections set forth in the Official Action, Applicants wish to review the subject matter of the current claims and the teachings of the specification.

Revised claim 13 is directed to an isolated peptide selected from the 14 mer fragment of the enzyme, acetylcholinesterase (AChE), as specified in SEQ. ID No. 1 (referred to herein below as "Synaptica Peptide") and functional variants of such fragment. The fragment is defined with reference to a structural requirement (see "(i) and (ii)" of amended claim 13) and a functional requirement (see "(iii)" of amended claim 13). The structural requirement corresponds to the peptide definition of original claim 1. The functional requirement reflects the peptide function specified in the Title of the specification and also finds support on page 6, lines 24-25, and Example 3 of the specification.

Example 3 describes electrophysiological studies which illustrate the ability of the claimed Synaptica Peptide to modulate induced calcium flux into neurons. It would be immediately evident to a person of ordinary skill working in the neuroscience field that the same experimental set up as described in Example 3 could, for example, be used to identify variants of Synaptica Peptide which retain its calcium channel modulatory function. Hence, Applicants believe that claim 13 is fully supported by the disclosure of the specification as filed and moreover provides a clear testable definition and thus scope, for variants falling within the claim.

As further described below, claim 13, as now amended, cannot be read to include the whole AChE. Further, it also cannot be read to include the β-amyloid precursor protein or any fragment thereof, including SEQ ID No. 2. It is important to note that on page 5, lines 23-25, of the specification, SEQ. ID No. 2 (the fragment of β-amyloid precursor protein explicitly mentioned on page 5) does not exhibit the calcium channel modulatory function of the claimed Synaptica Peptide. Such activity is also not a property of the whole AChE. Thus, it is clear that

the whole AChE and β-amyloid precursor protein or fragment thereof are excluded from the claims.

With regard to the rejection of claims 13-17 and 28-31 under 35 USC § 101, this rejection is deemed to be untenable and is thus respectfully traversed.

Applicants strongly believe that the Examiner has incorrectly concluded that the claimed peptide lacks either a specific and substantial, credible asserted utility or a well established utility. In setting forth this rejection, the Examiner has failed to properly analyze the teaching of the specification in light of the fact that there was much evidence available prior to the filing date of the present application to support that AChE has a non-enzymatic role (sometimes referred to as its non-classical role) in the brain and to link that non-enzymatic role with neurodegenerative disease causation, in particular, causation of Alzheimer's Disease, Parkinson's Disease and Motor Neuron Disease (see, in particular, paragraphs 1 and 2 on page 1 of the specification and the paragraph bridging pages 3 and 4; see also the appended review article of Professor Susan Greenfield from Spring Research News (1997)).

The interest in Synaptica Peptide arises since its identified biological activity, as illustrated by Examples 3 to 5, provides evidence that non-enzymatic function of AChE in the brain is mediated by an *in vivo* counterpart arising from processing of the enzyme. Example 3 importantly shows that Synaptica Peptide functions as a calcium channel modulator. This fits with processing of AChE underlying a trophic function in developing brains mediated by Ca^{2+} entry into immature neurones. It is believed that the same mechanism underlies the linkage of the non-enzymatic function of AChE with neurodegenerative disease causation in adult brains since

it is well known that calcium ions may be toxic to mature neurones at a level which is beneficial to developing neurones (see, in particular, the fourth paragraph in column 1 on page 3 of the appended review article).

In light of the evidence that Synaptica Peptide is a biologically active fragment of AChE, the inventors strongly believe that it has a credible utility as a research tool in, for example, identifying compounds of potential interest in the development of therapeutics to treat neurodegenerative diseases associated with non-enzymatic function of AChE. New claim 34, as presented above, is directed to such an application of Synaptica Peptide as a research tool. It is contended that this represents a specific, substantial and credible utility of Synaptica Peptide and functional variants thereof as claimed. Indeed, Synaptica Limited, the assignee of the present application, is a company founded on the recognition that Synaptica Peptide represents an important addition as a research tool to the furtherance of investigation of neurodegenerative disease causation and potential treatments for such diseases, in particular, Alzheimer's Disease, Parkinson's Disease and Motor Neuron Disease.

Since the filing of the Parent International Application, further information has been acquired by Synaptica Limited to substantiate that the biological activity of Synaptica Peptide is indeed a model for non-enzymatic function of AChE in the brain and that this function is of relevance to neurodegenerative disease causation. In particular, for example, a brain receptor for Synaptica Peptide has been identified which is consistent with the proposed mechanism for the non-enzymatic role of AChE in the brain. Furthermore, there has been further studies of the behavioural effect of Synaptica Peptide in rodent brains.

Thus, in light of the above, Applicants submit that Synaptica Peptide does have a specific and substantial, credible asserted utility in accordance with 35 USC § 101.

With regard to the rejection of claims 13-17 and 28-31 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable and is thus respectfully traversed.

Applicants believe that their arguments against the above 35 USC § 101 rejection is also applicable for this rejection. As stated above, since Synaptica Peptide is a biologically active fragment of AChE which functions as a calcium channel modulator, the claimed peptide can easily be used by one skilled in the art as a research tool in, for example, identifying compounds of potential interest in the development of therapeutics to treat neurodegenerative diseases associated with the non-enzymatic function of AChE. Thus, it is clear that the claimed peptide satisfies the "how to use" requirement under 35 USC § 112, first paragraph.

With regards to the functional variants of the Synaptica Peptide, as already stated earlier, such variants are now claimed with reference to both a structural requirement and a readily testable functional requirement. It is a simple matter for one skilled in peptide synthesis to make variants of a short peptide by routine chemical synthesis techniques. Furthermore, as previously highlighted above, Example 3 illustrates an experimental system whereby compliance with the functional requirement of claim 13 may be verified for any such variant. Other experimental systems might be employed on the basis of the disclosure of the specification. Obtaining species variants or allelic variants of a known DNA sequence is a very different matter from obtaining functional variants of a known biologically active peptide of 14 residues in length. Hence, Applicants strongly believe that given the limitations in the claims and the teachings of the

specification, an artisan would now only require routine experimentation to determine the functional variants of the Synaptica Peptide. As a result, Applicants respectfully request that this rejection cannot be sustained and should be withdrawn.

With regard to the written description rejection of claims 13-17 and 28-31 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable and is thus, respectfully traversed.

Under the new written description guidelines, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.

As stated earlier, the Applicants have defined the variants of the Synaptica Peptide by structure ("comprising at least 6 amino acid residues, and having at least 70% homology with part or all of the peptide of SEQ ID No. l") and by function (" retaining the calcium channel modulatory function of the peptide of SEQ ID No. l")

It is important to note that under the new guidelines, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. The structural and function description of the variants of the Synaptica Peptide was clearly set forth in the specification and original claims.

Thus, in view of the above, Applicants believe that the inventors were clearly in possession of the claimed invention in accordance with the requirements of 35 USC § 112, first paragraph.

With regard to the objection of claim 29 under 37 CFR 1.75(c), this objection has been rendered moot by the cancellation of the respective claim.

With regard to the rejection of claims 14-17 and 28-31 under 35 U.S.C. § 112, second paragraph, this rejection has also been rendered moot by the cancellation of claims 14, 17 and 29.

With regard to the rejections of the noted claims under 35 USC § 102(b) as set forth in items 14 and 15 of the Official Action, these rejections are deemed to be untenable and are thus respectfully traversed.

Under U.S. case law, to constitute anticipation of the claimed invention, a single prior art reference must disclose each and every material element of the claim. Here, in this case, neither of the references cited by the Examiner has any relevance to the peptides encompassed by amended claim 13.

The cited reference, de Serres et al., only discloses studies showing that previously proposed proteolytic activity of AChE against β-amyloid precursor protein (β-APP) is accounted for by contamination with trypsin. The only peptides disclosed in the reference are two amino terminal-extended fragments of β-APP and trypsin cleavage fragments of those peptides. None of those peptides represent variants of Synaptica Peptide as now claimed.

The first peptide mentioned on page 281 of the de Serres et al. reference overlaps with only the first 4 amino acid residues of the β-APP fragment specified in paragraph 3 on page 5 of

the subject application (SEQ ID No. 2) and the first three amino acid residues of Synaptica Peptide (SEQ ID No. 1). It is to be noted, however, that it has a far longer N-terminal portion which is completely irrelevant to SEQ ID No. 1. The second peptide mentioned on page 281 of the de Serres et al. reference ("de Serres peptide 2") overlaps with the final five amino acid residues of SEQ. ID No. 2. Only two of those amino acid residues (VH) overlap with SEQ ID No. 1 in the alignment given in Figure 1. The de Serres Peptide 2 contains far more sequence which is completely irrelevant to SEQ. ID. No. 1. Even SEQ ID No. 2 itself, which has far more homology with SEQ ID No. 1 than either of the peptide substrates mentioned in de Serres et al., does not exhibit the calcium channel modulatory function of SEQ ID No. 1 (see again lines 23 to 24 on page 5 of the specification).

It appears that the Examiner has read previous claim 13 to cover the whole acetylcholinesterase. It is important to consider that the functional requirement specified in amended claim l3 (activity as a calcium channel modulator) is not shared by the whole AChE. Indeed, as previously emphasized above, the interest in the claimed Synaptica Peptide arises since its identified biological activity provides evidence that the non-enzymatic role of AChE in the brain is mediated by an in vivo counterpart arising from the processing of the enzyme. As indicated on page 4, lines 24-25, of the specification, Synaptica Peptide corresponds to residues 535-548 of human AChE. This region is a part of the C-terminal tail region of AChE believed to be responsible for holding monomers of the enzyme in tetrameric form. Whole acetylcholinesterase is a large enzyme and would not normally be classified as a peptide. In any case, the functional requirement in amended claim 13 makes it inconceivable that the claim could

be correctly read as encompassing the parent protein from which Synaptica Peptide is derived. Any data which purports to refer to whole AChE as having calcium channel modulatory ability could only be accounted for by some fragmentation of the enzyme in the experimental system of concern.

With regard to the Moran et al. reference, this reference does not teach or suggest any peptide fragment of AChE. The only peptide referred to in this reference is an N-terminal fragment of β-amyloid protein which was used to obtain a monoclonal antibody. The monoclonal antibody was used to demonstrate colocalization of protein recognized by the monoclonal antibody with acetylcholinesterase and butrylcholineserase in brain section plaques. Such studies do not disclose the peptide as now claimed or assist in any way the selection of such a peptide from a complete AChE protein sequence.

Thus, in light of the above, Applicants submit that these rejections can no longer be sustained and should be withdrawn.

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of

this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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SPRING Research News

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PARKINSON'S DISEASE: A CASE OF TOO MUCH TOO LATE?

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In Parkinson's disease, the chemical messenger dopamine is abnormally low in the brain, due to the progressive loss of a specific population of brain cells (nigrostriatal neurones). Current therapy thus quite logically focuses on increasing the availability of this key transmitter. However drugs that enhance the production of dopamine (L-Dopa), or prevent its immediate destruction (deprenyl), or simulate its action (pergolide), in no instance actually arrest the degenerative process. Many research groups are therefore looking beyond the manipulation of dopamine itself, in an attempt to develop a better therapy. In many cases these new initiatives aim to resolve the problem 'downstream' of the original loss of the cells, either by targeting what causes the cells to die, or by encouraging new cells to grow in place of the dead ones. Our group, however, is taking a different line of attack, by adopting an 'upstream' strategy, where we are trying to identify why the cells have died in the first place.

Many of us have a relative or friend who has made a partial or sometimes even a seemingly complete recovery from a stroke. Indeed, it is widely acknowledged that after destruction of certain populations of neurones, neighbouring cells can 'take over' the function of the dead cells, to greater or lesser extents. So we know that damage to a neuronal population does not always result in the devastating progression of loss of the remaining cells, that is so tragically the hallmark of Alzheimer's and Parkinson's diseases.

What might be special about the vulnerable cells?

The neurones lost primarily in Parkinson's disease can be classified as part of a larger group of cells in the brain that have properties distinct from most other neurones. This larger group is situated in the brain as a kind of continuous hub, extending from the top of the spinal cord through to the lower part of the front of the brain (basal forebrain). Other cell groups within this hub include those that do not use dopamine, but rather a range of chemically related transmitters such as noradrenaline and serotonin. Interestingly enough, these neurones can also be affected in Parkinson's disease.

There is also another chemical used by another group of cells within the hub: acetylcholine. Loss of these particular neurones is this time related to that other neurodegenerative disorder, Alzheimer's disease. Most therapeutic strategies treat these two major instances of neuronal degeneration as distinct disorders, which, of course, they are. Since each different region within the hub will be in contact with other different brain regions, it is hardly surprising that the symptoms arising when such complex circuitry is disrupted, will be different. But it is possible that the resulting difference in symptoms and indeed favoured drug treatment, which in turn targets the salient deficient transmitter, - acetylcholine for Alzheimer's disease, dopamine for Parkinson's disease, - is *incidental* to a much more basic factor, a shared similarity between the different populations of cells within the hub.

Supporting this idea, which was first proposed in the early 1980s, is the fact that Alzheimer's disease and Parkinson's diseases can co-exist. Over the last 15 years however, diverse data from many laboratories has enabled us to build up a profile of normal function in these neurones within the hub. Very briefly, these cells appear to function throughout the brain. If we look at the way the connections are organised, then it becomes clear that unlike most neuronal circuits where transmitters are released in a highly local and precise manner, the transmitters dopamine, noradrenaline, serotonin and indeed acetylcholine, are in each case released from connections emanating from

(Continued on page 3)

(Continued from page 2)
the hub, and targeting the rest of the brain, the so called 'higher centres' in a diffuse fashion, more reminiscent of fountains.

A second difference is that, unlike many cells in the brain, these neurones are spontaneously active, suggesting in turn that they themselves might not have a highly detailed and precise action, but might act to bias and enhance responses in the more sophisticated neurones throughout the brain with which they make a secondary contact.

However a third difference is perhaps the most relevant to tracking down an important factor in neurodegeneration. Unlike other neurones in the brain, the cells in the hub can, to a certain extent, regenerate following damage in adulthood. Could this difference account for why damage here leads to neurodegeneration whereas in other neurones, say those affected in a stroke, it does not?

It is a counterintuitive idea that neurodegeneration might be an aberrant form of development, that a process so clearly valuable for the developing brain, should be at the same time so pernicious in maturity. However there is a critical difference. In both cases, the sprouting of new connections between neurones requires the entry into the cell of calcium ions. In development, it turns out, neurones can mobilise and cope with calcium far more efficiently than their mature counterparts. Indeed, it has been shown quite recently that the same amount of calcium that will be beneficial in developing neurones, will kill cells a little older.

Cell Death

So perhaps neurodegeneration occurs when a few cells in the hub are initially damaged. As a result the neighbouring cells attempt to send out new connections, but in so doing instigate further death. The initial location of damage within the hub, and the extent of that damage would determine whether the problem is realised as Alzheimer's or Parkinson's disease, and indeed whether the two conditions coexist. The resulting secondary damage seen to other cells outside of the hub, when dementia occurs, would be due to the fact that the neurones on to which the hub make contact, are in turn affected as a secondary consequence.

One possible therapy might be thus to reduce calcium entry into these neurones. However, since all brain cells require calcium to function properly, this treatment would be too non-specific. Instead we need to reduce the calcium entry only in the particular scenario, and in the particular cells, where there is attempted regeneration.

Preventing further deterioration

Our group is exploring a possible site-specific candidate chemical that, we believe, might be critical in the process whereby the neurones in the hub develop and indeed attempt to regenerate. Despite the fact that subpopulations of neurones in the hub use different transmitters, they all have one chemical in common. This substance is well known as an enzyme that is important in the systems using acetylcholine, indeed it is named acetylcholinesterase (AChE). However, for many years now we have been working on the idea that AChE can have a function totally unrelated to its normal role. After all, AChE is found throughout the hub, in neurones that do not use acetylcholine, such as the dopamine cells of the substantia nigra. Already, we have shown that AChE can indeed be released in the process of the development of young cells, by enhancing calcium entry.

If AChE is really a critical link in enabling certain key cells in the brain to develop, and if degeneration is an aberrant form of development, then it follows that a novel, valuable way of arresting the progressive death of cells, would be to block this non-classical action of AChE. As soon as the disorder had been diagnosed, the dream would be to offer patients the prospect, not necessarily of complete recovery, but the assurance that their condition was not going to deteriorate any further. There are still many 'ifs' to our reasoning, but this approach might eventually be yet another weapon in the pharmaceutical armoury against Parkinson's disease.

Apart from her primary work in neurodegeneration, Professor Greenfield contributes to the public understanding of science. She writes a fortnightly column for the Independent on Sunday. Among other books she will be publishing in Penguin in 1998, a sequel to her theory of consciousness 'Journey to the centres of the mind' published by W H Freeman